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FOOD AND DRUG ADMINISTRATION

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

GENERAL AND PLASTIC SURGERY DEVICES PANEL

OF THE MEDICAL DEVICES ADVISORY COMMITTEE

OPEN SESSION

60th Meeting

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Robert L. McCauley, M.D.
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Nancy A. Dubler, LLB
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LeeLee Doyle, Ph.D.

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Debera M. Brown

C O N T E N T S

P R O C E E D I N G S

Call to Order and Conflict of Interest

DR. KRAUSE: I think we have reached critical mass so we can start the open session of the panel meeting. Good afternoon, everyone. We are ready to begin the 60th meeting of the General and Plastic Surgery Devices Panel.

I am David Krause and I am the executive secretary of this panel and also a reviewer in the Plastic and Reconstructive Surgery Devices Branch, in the Division of General and Restorative and Neurological Devices.

I would like to remind everyone that you are requested to please sign in on the attendance sheets, which are available at the tables just outside the door. You may also pick up an agenda, panel meeting roster and information about today's meeting at those tables. The information includes how to find out about future meeting dates through the advisory panel phone line and how to obtain meeting minutes or transcripts. This and other panel meeting information, including panel meeting summaries and transcripts, are now also available on the worldwide web. Advisory panel meeting activities are available by clicking on the CDRH

home page from the FDA website, which is www.FDA.gov. By clicking on premarket issues and then advisory committees, the summaries, transcripts and other advisory committee material section may be accessed. You can then access the CDRH advisory committee database.

Before turning this meeting over to our Chairman, Dr. Whalen, I am required to read two statements into the record. First I will read the conflict of interest statement into the record:

The following announcement addresses conflict of interest issues associated with this meeting, and is made part of the record to preclude even the appearance of an impropriety. To determine if any conflict of interest existed, the agency reviewed the submitted agenda and all financial interests reported by the committee participants. The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employers' financial interests. However, the agency has determined that participation of certain members and consultants, the need for whose services outweighs the potential conflict of interest involved, is in the best interest of the

government.

Therefore, waivers have been granted for Drs. Michael Choti and Michael Miller for their financial interests in and firms at issue that could potentially be affected by the panel's recommendations. The waivers allow these individuals to participate fully in today's deliberations. Copies of these waivers may be obtained from the agency's Freedom of Information Office, Room 12A-15 of the Parklawn Building.

We would like to note for the record that the agency took into consideration certain matters regarding Drs. Choti and McCauley. These panelists reported current interests in firms at issue but in matters that are not related to today's agenda. The agency has determined, therefore, that they may participate fully in all discussions.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participant should excuse him or herself from such involvement and the exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that all persons

making statements or presentations disclose any current or previous financial involvement with any firm whose products they may wish to comment upon. Thank you.

The second statement I am going to read into the record is the temporary voting memo. This is a memo that is signed by Dr. Feigal who is the Director of the Center for Devices and Radiological Health:

Pursuant to the authority granted under the Medical Devices Advisory Committee Charter, dated October 27, 1990 and as amended August 18, 1999, I appoint Nancy Dubler and Amy Newburger as voting members of the General and Plastic Surgery Devices Panel for this meeting, on July 8 and July 9, 2002.

For the record, these individuals are special government employees and consultants to this panel or other panels under the Medical Devices Advisory Committee. They have undergone the customary conflict of interest review, and have reviewed the material to be considered at this meeting.

At this time, I would like to turn the meeting over to our Chairman, Dr. Tom Whalen.

DR. WHALEN: Thank you, Dr. Krause. Good afternoon. My name is Dr. Thomas V. Whalen. I am the chairperson of the General and Plastic Surgery Devices Panel.

Today the panel will be making recommendations to the Food and Drug Administration on the classification of silicone elastomer for scar management devices and on the proposed reclassification of absorbable hemostatic agents and dressings from Class III to Class II. I would like to note for the record that voting members present constitute a quorum, as required by 21 CFR Part 14.

Before we begin this meeting, I would like to ask our distinguished panel members, who are generously giving their time to help the FDA in the matters being discussed today, and the other FDA staff seated at the head table to introduce themselves. I would ask that each state their names, affiliations and positions and area of expertise, starting to my right with Dr. Witten, please.

Introductions

DR. WITTEN: I am Dr. Celia Witten, division director of the Division of General and

Restorative and Neurological Devices at FDA, which is the reviewing Division for these products.

DR. DEMETS: I am David DeMets. I am professor and chair of the Department of Biostatistics and Medical Informatics at the University of Wisconsin, in Madison. I am a statistician by degree and have been involved in clinical trials for a long time.

DR. CHANG: I am Phyllis Chang, associate professor in the Division of Plastic Surgery and also in the Division of Hand and Microsurgery for the Departments of Surgery and Orthopaedic Surgery at the University of Iowa. I am an FDA panel member.

DR. MILLER: I am Michael J. Miller. I am an associate professor of Plastic Surgery at the University of Texas, MD Anderson Cancer Center.

DR. NEWBURGER: I am Amy Newburger. I am a dermatologist in New York, in private practice, and I am an attending physician at White Plains Hospital Medical Center, and I teach at St. Luke's Roosevelt Medical Consortium.

DR. KRAUSE: I am Dave Krause.

DR. CHOTI: I am Michael Choti, associate professor of surgery at Johns Hopkins University in

Baltimore, Maryland, and I am a general surgeon and surgical oncologist.

DR. DUBLER: I am Nancy Dubler. I am trained as an attorney. I direct the Division of Bioethics at Montefiore Medical Center, and I am a professor of epidemiology and social medicine at the Albert Einstein College of Medicine.

DR. MCCAULEY: Robert McCauley, professor of surgery and pediatrics at the University of Texas Medical Branch, and chief of plastic surgery services for the Shriner's Burn Hospital.

DR. DOYLE: I am LeeLee Doyle. I am a professor of obstetrics and gynecology, and associate dean for continuing medical education and faculty development at the University of Arkansas for Medical Sciences, College of Medicine, and I am the consumer representative on the panel.

MS. BROWN: I am Debera Brown. I am the vice president of regulatory affairs for Broncus Technologies, which is a medical device company. I am also the industry rep on this panel.

DR. WHALEN: As stated, my name is Dr. Thomas Whalen. I am chief of the Division of Pediatric Surgery and professor of surgery and pediatrics at Robert Wood Johnson Medical School in

New Brunswick, New Jersey.

Before we continue with the classification and reclassification portion of the hearing, we will have Mr. Anthony Watson, acting branch chief of the Plastic and Reconstructive Surgery Devices Branch, provide an update on general and plastic surgery device activities since the last meeting. Mr. Watson?

Panel Update

MR. WATSON: Thank you, Dr. Whalen, and good afternoon. I am Anthony Watson, the acting branch chief of the Plastic and Reconstructive Surgery Devices Branch at FDA. Welcome, members of the panel, members of the public and manufacturers to this two-day meeting of the General and Plastic Surgery Panel.

This panel last met on July 17, 2001 and recommended approval of Ortec's PMA application for OrCel Bilayered Cellular Matrix for use on donor sites on burn patients. The agency approved this product on August 31, 2001.

On November 19, 2001, the agency approved a PMA application for Lifecore's Intergel Adhesion Prevention Solution. This application was reviewed by this panel at the January, 2000 panel meeting

and was recommended to be not approvable. The agency agreed and, after receiving a not approvable decision, the sponsor requested review at the newly formed Medical Device Dispute Resolution Panel. This panel met on September 6, 2001 and recommended that the application be approved.

On June 18, 2002, the agency released an updated guidance document, entitled, "Guidance for Resorbable Adhesion Barrier Devices for Use in Abdominal and/or Pelvic Surgery."

Today, you will make classification recommendations to the agency on two types of medical devices: the silicone elastomer for scar management and the absorbable hemostatic agent and dressing intended for hemostasis during surgical procedures. Tomorrow the panel will be presented with an update of the conditions for approval for the two saline-filled breast implants approved in May of 2000. As a reminder, tomorrow we will not be discussing silicone gel-filled breast implants, and I request that panel members and members of the public limit their comments to saline-filled breast implants.

Panel members, we appreciate your commitment. Members of the public who have

requested time to address the panel, we appreciate your comments. Manufacturers, we appreciate your participation in presenting the information you have to the panel and answering questions that the panel may have. Thank you for your attention.

DR. WHALEN: Thank you, Mr. Watson. We will now proceed with the first open public hearing session of this day. I would ask at this time that any and all persons addressing the panel, please come forward, speak clearly into the podium microphone as the transcriptionist is dependent upon this to provide an accurate record of this meeting.

We are requesting that all persons who make statements to the panel during the open public hearing portion of the meeting disclose whether or not they have financial interests in any medical device company whatsoever. Before making your presentation to the panel, in addition to stating your name and affiliation, please state the nature of your financial interests and if you have none, please so state. Is there anyone who wishes to address the panel? Please indicate by show of hands.

Since there are no requests to speak in

the open public hearing, we will now proceed to the open committee discussion. At this time, we will begin the discussion with the classification of silicone elastomer for scar management. We will start with the presentation by Mr. Mark Dillon, president of Bio Med Sciences. This will be followed by a presentation by Mr. Carey Rehder, plastic reconstruction division engineering manager of PMT Corporation, who will be followed by Mr. Tom Fallon and Mr. Mike O'Brien, of ReJuveness Pharmaceuticals.

The FDA presentation and a reading of the FDA questions will follow the industry presentations. We will then have a general panel discussion of this topic, followed by a more focused panel discussion aimed at answering FDA's questions.

Following the panel discussion, we will complete the reclassification worksheet and supplemental worksheet. The vote on these worksheets will constitute the panel's recommendation to the FDA.

I would like to remind public observers at this meeting that while this portion of the meeting is open for public observation, public attendees

may not participate except at the specific request of a panel member. If any of the industry representatives addressing the panel have copies of the remarks that they are making to us today, it would be greatly appreciated if they could pass them to the transcriptionist so that accuracy can be assured in what you are bringing to us today. We will begin with Mr. Dillon's presentation.

Classification of Silicon Sheeting for Scar Management Industry Presentation

MR. DILLON: Thank you very much, Dr. Whalen. I am Mark Dillon, the president and founder of Bio Med Sciences. We have been marketing silicone-based products for scar management since the early 1990's.

As we are all aware, these are products that are used for the prevention and reduction of hypertrophic scars and keloids. It is my opinion that these devices have substantial importance in preventing impairment of human health and present a potential risk of illness or injury if misused. I think it is common knowledge that some devices are intended for lay use instead of use by healthcare professionals.

I, therefore, believe that these products

should be classified as Class I, reserved or non-exempt, therefore, requiring a 510(k) notification. I have several reasons for this position. First, there is a wide variety of devices that are on the market. There are rigid, non-adhesive silicone elastomer materials and these generally require some type of tape to hold them in place. There are also adhesive gel type products. Some of these contain other materials as an embedded mesh or some type of reinforcing mechanism. There are past products that are essentially massaged onto the surface of the scar. There is even one product that I am aware of that is a silicone gel-filled cushion that is indicated for this purpose. There are also mineral oil-based materials that are silicone-containing, as well as products that are called tri-block copolymer compounds. In addition, there are a number of composite type structures such as splinting materials that are lined with silicone, padding type products and even textiles that are laminated to silicone.

I think that there are likely to be new designs and new products that are introduced to the market, and I think it would be difficult to show

substantial equivalence without having some type of review process involved with that.

Another consideration is the indications for use. Some of these products are marketed strictly for cosmetic purposes, but others are marketed more for a professional audience, for use with burn patients. Functionality and the patient's health is a critical issue. Furthermore, I think that there has been a wide variety of claims that have appeared in the marketplace with these types of products. I have seen over the years products that claim to heal scars or are even positioned as an alternative to surgery. Likewise, I think these claims should be confirmed through the 510(k) process.

Additionally, I believe there are some risks involved with the use of these products. I think patients need to be adequately warned not to use these products on open wounds. Also, there is a possibility of skin irritation or rash, particularly with some of the products that require use of adhesive tape or contain other materials, other than silicone. Lastly, I think that some of these products can be positioned to discourage adequate professional supervision or compliance.

Therefore, my concern is that without the premarket notification system some devices may emerge in the marketplace that are not substantially equivalent, are positioned with inappropriate indications and claims, and may pose undue risk, including the discouragement of professional supervision when appropriate. Thank you.

DR. WHALEN: Does any panel member have a question for Mr. Dillon?

[No response]

Thank you, sir.

MR. DILLON: Thank you very much.

DR. WHALEN: We will now continue with Mr. Rehder's presentation, if Mr. Rehder is available.

[Mr. Rehder is not present]

Very well, the final identified industry speakers today jointly are Mr. Fallon and Mr. O'Brien.

MR. FALLON: Hello, panel. Thank you for letting me speak today. My name is Tom Fallon. I am president of ReJuveness Pharmaceuticals. We market a silicone sheeting product for hypertrophic and keloid scarring.

I would like to address the proposed

regulation identification in two parts. A scar management device is a silicone sheeting product intended for use on uncompromised skin for scar management.

The first part--a scar management device is a silicone sheeting--we fully concur with this identification. Silicone should not be treated as some homogeneous category. Only silicone sheeting has been demonstrated to be effective on problem scarring. The oil and liquid forms of silicone have never been shown, in any peer-reviewed study that I know of, to be effective and are potentially toxic. The difference between the two, as we see it, is that the silicone sheetings give off silicon when hydrolyzed. The silicone oils do not. They give off just silicone.

We fully agree with the first part; we fully disagree with the second part of the identification--intended for use on the uncompromised skin. The skin covering keloids and hypertrophic scars seems to be compromised in every way but appearance. The FDA's position is that the skin is not compromised because it is visually intact. We admit that it seems ironic but the functional measures of the stratum corneum covering

these scars have been demonstrated to be compromised in three ways.

In a study of the functional analysis of the stratum corneum in scars, which I have included in the package that I recommend you read, it was shown that these problem scars yield the same measures as open blister wounds in the categories of transepidermal water loss, electric conductivity and stratum corneum turnover rates. They are four times higher in keloid and hypertrophic scars as they are in atrophic scars and normal skin. Since scar management refers to hypertrophic and keloidal scars and not to atrophic scars, we would have to conclude that scar management refers to compromised skin.

I also include a couple of papers by Dr. Peter Elias and his group, out at the University of San Francisco Veterans Administration Hospital. It demonstrates the theories emerging centering around the driving function of the stratum corneum and many maladies of the skin once thought to be originating in the dermis.

In "The Mystery Widens" he applies the skin-drive principle to hypertrophic scars and keloids. Another paper included is the

"Investigation of the Keloid-Derived Keratinocytes on Fibroblast Growth." It demonstrates that the production of collagen in keloidal and hypertrophic scars is caused by the compromised skin covering them.

Our proposed mechanism of action is taken from a paper, "Hypertrophic Scars and Keloids: Immunophenotypic Features and Silicone Sheets to Prevent Recurrences." In this study they took 20 keloidal scars, excised them and in ten of them they put silicone sheeting over them; in the other ten they put nothing. In nine of the ten of the scars without the silicone sheeting keloid scars came back. Almost all of them, except four, under the silicone sheeting the scars came back.

They did immunophenotypic analysis and they found the scavenger receptor CD36 in large amounts under the silicone sheeting. These scavenger receptors are essential in rebuilding the stratum corneum. The most important component of the stratum corneum is cholesterol. It is not effective when applied topically, and it is transported by these scavenger proteins from high density lipid proteins to the stratum corneum. So, with the proposed identification it will be quite

difficult to make the correct structure, function and mechanism of action claims.

The last paper that I have included is release and distribution of silicone-related compounds in the skin exhibits the release of silicon from silicone sheeting into a buffer solution and into normal and keloidal skin. If silicon is the active ingredient, then there are dosage and shelf-life issues.

We did our own study, which is also included in the packet, where we put ReJuveness Spenco gel sheeting in ten-year old Cica-Care under the same testing, and what we found was that the rates of silicon release were different for different sheetings, and in the ten-year old Cica-Care there was no silicon released at all.

In conclusion, we feel as though the silicone sheeting is completely safe and that it should be a Class I but that the scars that it is addressing, hypertrophic and keloid scars, are composed of compromised skin and it is the driving mechanism in these maladies. That is it.

DR. WHALEN: Are there questions for Mr. Fallon?

MS. BROWN: I have a question. You

proposed Class I. Would that be with or without a 510(k)?

MR. FALLON: I would say with a 510(k).

MS. BROWN: Thank you.

DR. WHALEN: With your objection to the second part to what has been proposed, is your statement in the center of your third page what you are proposing as an alternative wording, "scar management device...?"

MR. FALLON: I really didn't know if we were going to participate on that level to suggest what the wording should be until yesterday. So, yes, I think that it should be changed. I mean, if you would like a suggestion from me, I just need probably a day or two where I could come up with a suggestion.

DR. WHALEN: But your viewpoint or your company's viewpoint is that focally hypertrophic scars and keloids are not uncompromised skin. You are not saying to the panel that you think we should consider applying this on open wounds, fresh wounds in the operating room when we have just made an incision, etc.?

MR. FALLON: Well, I really don't see why not; I don't see why they shouldn't be applied to

open wounds. In the Italian study, where they put it over excised keloids, they do put it on excisions that were open. They did it prophylactically. So, I they are safe enough, yes, to put on open wounds and perhaps that would be a different classification for that use.

DR. WHALEN: Any other questions? Dr. Miller?

DR. MILLER: Thank you for your presentation. I just want to make sure I am clear about what you are calling an open wound. I mean, when I think of an open wound I think of a wound where the epithelium is not in contact across the wound; you have exposed tissue below the epithelial level that is exposed.

MR. FALLON: Right.

DR. MILLER: So, your thought is that it is okay. You would suggest that we can place these devices on those types of wounds?

MR. FALLON: If they are properly sterilized, yes. I mean, I don't know what effect they would have on open wounds. I know they work on ulcerated wounds, and keloid and hypertrophic scars are very similar to an ulcerated wound in that they are microvascularly cut off. Keloid and

hypertrophic scars are composed of essential fats, basically fats. So, the difference between the two is slight.

DR. WHALEN: Dr. Newburger?

DR. NEWBURGER: Excuse me, have you see any evidence of any type of foreign body reaction from the silicon which is released from the gel across this compromised epidermis?

MR. FALLON: Yes, we have had a couple of reports of women using the sheeting applied to the scars after breast implantation. I don't know if there is something going on between them, but we have had several complaints on that. But, for the most part, we have sold over 100,000 of these devices and we have had basically no complaints, just the tape occasionally.

DR. NEWBURGER: I am asking specifically about a foreign body reaction as opposed to an irritation or a folliculitis and occlusion. In other words, here is a molecule that is going through the compromised epidermi, are you getting a soft tissue reaction in the dermis with foreign body cells?

MR. FALLON: I don't know that exactly. Our scientific advisor is Dr. Arthur Brawer, who is

a noted expert on silicone. But it basically is like coal miner's disease, that is, the action of the silicone sheeting on the hypertrophic scar. It goes down as an antigen, stimulates the scavenger CD36 and marshals them to the site, it seems, and then from there they are able to produce and serve their many different functions, versatile functions that they are able to do--transporting cholesterol, essential fatty acids, as well as taking away excess materials in the extracellular matrix. So, that is what we think is going on.

DR. WHALEN: Mr. Fallon, are your remarks everything or is Mr. O'Brien still going to be speaking?

MR. FALLON: Oh, Mr. O'Brien couldn't show, I am sorry.

DR. WHALEN: Thank you. We will continue now with the FDA's presentation with Dr. Sam Arepalli.

FDA Presentation

DR. AREPALLI: Good afternoon. We are here this afternoon to seek a panel recommendation to classify scar management devices indicated for management or scars. My name is Sam Arepalli, reviewer in Plastic and Reconstructive Surgery

Branch, Division of General, Restorative and Neurological Devices. I will be presenting device identification and health risks aspects of the device. Reviewers from the Office of Surveillance and Biometrics, CDRH are in the audience to clarify any questions regarding Medical Device Reports. After my presentation, Ms. Marjorie Shulman will walk you through the classification worksheets.

This slide is on regulatory history. As you know, medical devices are classified into three classes, namely, Class I, Class II and Class III. Examples of Class I exempt products include hydrogels or hydrogel wound dressings and manual surgical instruments. Class II devices include implantable surgical meshes and sutures. Examples of Class III devices are interactive wound dressings and barriers.

At the time of the Medical Device Amendments of 1976, a few medical devices were unclassified. They include devices like scar management devices, the one that we are going to discuss today. They were unclassified. These devices are currently regulated as unclassified devices. The FDA has been making efforts to classify and reclassify medical devices since 1976

into the lowest regulatory class that can reasonably assure safety and effectiveness of their intended use.

I would like to bring to your attention that the same panel several years ago provided a recommendation to classify non-interactive wound dressings. This slide gives a brief description of the proposed identification of the device: A scar management device is a silicone sheeting product intended for use on uncompromised skin for scar management.

This slide gives a brief description of FDA-cleared scar management devices. FDA has regulated silicone sheeting intended for scar management as an unclassified pre-amendment device. It has been cleared for marketing under several names. They are silicone sheeting, silicone elastomer and silicone gel for hypertrophic and keloid scar management. Also, the agency cleared a hydrogel for the same intended use.

There are about 75 scar management devices on the market. We searched the Medical Device Reports database for device adverse events. Two adverse events were found. The first adverse event, reported in January of 1998, was a

significant blistering caused shortly after using gel sheeting followed by full-thickness skin necrosis due to secondary infection. The blistering was not at the site of the gel sheeting application but in the areas nearby. It was determined by the reporting physician that the event was unrelated to the device but we could not rule out the possibility that the device was involved.

The second adverse event, reported in June, 2001, was an allergic reaction following the use of silicone sheeting. Following 39 hours of continuous use, the patient developed a severe red rash and flaky rough skin. This was determined as an isolated event and not likely that it was due to the use of the device. Some possible causes for the reported incident may be a reaction to the tape used to hold the sheeting in place or moisture created under the silicone sheeting after wearing the product for such an extended period of time.

This slide is the questions to the panel. Can I read them out?

DR. WHALEN: I will just interject that we will not be answering the questions at this time; we will at a later point in time, but please do

proceed, if you would.

DR. AREPALLI: Thank you. We have these two topics for panel discussion. Following this, Ms. Marjorie Shulman will walk you through the classification work sheet. Here are the two issues:

Please discuss the proposed classification for the scar management device for the management of hypertrophic and keloid scars. Also, discuss what descriptive information and intended use should be included in the proposed classification identification.

Number two, please discuss the risk of possible adverse skin reaction due to lack of biocompatibility for the scar management device and identify any other risks to health for these devices. Thank you. Marjorie?

Panel Discussion

DR. WHALEN: Just a moment, does any of the panel members have questions of Dr. Arepalli on his presentation?

[No response]

Thank you. We will get to Ms. Shulman in a moment but we are going to have a general discussion first. Are there comments or questions

of any of the panel members about what we have just heard on these devices? If I could kindle the fire by asking Dr. Chang if she has any comments on the subject that was raised about intact skin.

DR. CHANG: I have a comment and a recommendation for the panel to consider which is, rather than saying that this management is for uninjured skin, to describe it as that it should be intended for closed or intact skin, "closed, intact skin" as a replacement for the wording "uninjured" because, by definition, we are--

DR. WHALEN: Uncompromised.

DR. CHANG: Yes, uncompromised. We are proposing this device for scar which is not the same as uninjured skin.

The other question I had would be to ask Dr. Newburger's opinion regarding whether or not a skin rash could occur at a site distant from where this product might be applied. In other words, what is the potential for development of a rash to be related to use of a gel padding in one location and seeing a rash appear at a different site in the body?

DR. NEWBURGER: To my knowledge, the issue of silicones and true allergic reactions is pretty

well limited to foreign body reactions. We use various types of silicone gel sheeting in our practice and we have never seen a true allergic reaction to it, and you might say, well, in a private practice how substantial is this? Well, we have over 30,000 patients and we are using it multiple times every week and we have never seen a true allergic reaction. We have seen folliculitis. We have seen irritant reactions. We have seen problems with tape. But when we are putting it over skin which has healed over, and that is the only time we use it, we have not seen allergic contact dermatitis, nor have we seen distant reactions.

We have had a number of patients who have had solid silicone implants and we have seen distant reactions which have been identified as silicone granulomas. So, I am a little concerned about this information that silicone is actually released into the scar tissue. This is new to me and I thought I had read rather extensively on the area. I am concerned about that possibility. Certainly, the identity is not the same as you are going to see in the solid silicone rubber implant, which is what we have seen occur, but this raises

more questions to me rather than fewer.

DR. WHALEN: Dr. McCauley?

DR. MCCAULEY: One of the things that we actually think about when we are using these types of products is that we actually talk about using them in hyperproliferative scar disorders, which keloids and hypertrophic scars fall under. I guess that would distinguish it from some of the other hyperproliferative skin disorders that occur without trauma and that occur in dermatology. But I would propose that actually rather than say "uncompromised skin" we actually focus in on hyperproliferative scar disorders which hypertrophy scars and keloids represent.

DR. WHALEN: Dr. Witten, if I could ask a question, it strikes me that if FDA were going to be considering the use of this product on an open, fresh wound that it would go well beyond the scope of a reclassification or classification type of process. Am I correct in that? Would that require some other initiative on the part of a manufacturer or sponsor wishing to have that indication?

DR. WITTEN: Well, we are really asking you to classify what we have actually seen or cleared, which have been these devices for scar

management.

DR. WHALEN: But within the scope of what we are classifying, we are going to be defining the safety and efficacy of the product with its intended use in mind. So, are we at liberty in a classification hearing to be considering a broad scope of indications?

DR. WITTEN: We are only asking you to consider the scope of indications for which we have cleared the product.

DR. WHALEN: Thanks. Other issues or points? Dr. Miller?

DR. MILLER: Yes, I would like to emphasize that I think this product should probably not be used on an open wound. It is a very different situation than a closed wound with hypertrophic scarring and I think that should be emphasized. The use should be limited. I like the words of an intact wound, an epithelialized wound or a closed wound. I agree, uncompromised skin is not very precise but, certainly, it needs to be a closed wound.

DR. WHALEN: Any other comments specifically on the semantics of the indication or any of the issues that have been brought up?

DR. CHANG: I would like to second and ditto Dr. Miller's comments that this should be limited to closed, intact skin and not be placed on an open wound.

DR. WHALEN: Dr. Witten?

DR. WITTEN: Yes, I just wanted to say what Mr. Hurts clarified for me. Actually, I should have remembered to say this, but we already have a classification for open wounds. I mean, there are Class I exempt wound dressings for open wounds. So, there already are classifications for products intended for open wounds; they would already fit into a different classification.

DR. WHALEN: Is there a consensus on the wording, that we are going to go forward with? Are we are going to say closed wounds or, Dr. McCauley, if you could say it again?

DR. MCCAULEY: Closed hyperproliferative scar disorders.

DR. WHALEN: That implies that you are talking about closed wounds.

DR. MCCAULEY: Right.

DR. WHALEN: Are there any other comments?

[No response]

Then, at this time we would like to begin

to focus our discussion on the FDA questions that Dr. Arepalli has brought forward to us and that remain projected on the screen. At this time we will not refer to the reclassification questionnaire. We will do that after this discussion that is focused upon those questions. Please consider, panel members, the silicone elastomer for scar management device wile responding to the questions before us taken one at a time.

The first question again, discuss the proposed classification for the scar management device for the management of hypertrophic and keloid scars. Also, discuss what descriptive information and intended use should be included in the proposed classification identification.

Dr. McCauley, would you care to start off on that one?

DR. MCCAULEY: First, I would like to have some comments. Basically, this is related to the information which has been presented to us relative to this whole classification of silicone polymers.

Number one, they have been around for quite a while and, number two, they have not, in my opinion, posed a significant danger, if you will,

to patients. However, what bothers me is the fact that there are a number of studies which have been published that are, number one, anecdotal or, number two, if they have been controlled, randomized studies they are very small. Number three, the mechanism of action for these materials really has not been clarified.

I think that is very important in our deliberations in terms of exactly how you want to classify these devices. If you say that silicone leaches out of these polymers into the wound and affects CD36 cells, then you are really talking about something that is more interactive and something that may be classified as a Class III.

If you feel that the silicone in and of itself is non-interactive but that it achieves this effect just by coverage, although we know it is probably not pressure that gives this effect, there is some controversy in terms of whether temperature really matters. Some studies by Lee suggest that two degrees centigrade elevation in the temperature underneath these materials causes a tremendous increase in the action of collagenase, which is how these effects are achieved. Other studies have not shown that. Other studies have said that hydration

may be the mechanism by which we see improvement in the wounds.

But I think it is very important to try to decide what is the mechanism of action before we can actually properly classify these compounds.

DR. WHALEN: Just to play the devil's advocate, if these have been in use for so many years and, in your opinion, you say you feel pretty much that they are safe, from a pragmatic point of view do you think it is that critically important after all these years to delineate that mechanism of action?

DR. MCCAULEY: I think it is important to delineate that. Whether or not that is important enough for classification, I think if we consider the fact of this new data which was presented relative to the leaching of silicone out of the compound into the wound, I think that is a little disturbing to me.

DR. WHALEN: Dr. Dubler, any comments?

DR. DUBLER: Dr. McCauley, in the study that showed there might be some leaching of the silicone into wounds---

DR. MCCAULEY: I am sorry, this is information that was just provided to us by Mr.

Fallon.

DR. DUBLER: That is right, because there are no published studies that we have reviewed that have indicated that.

DR. MCCAULEY: Exactly.

DR. DUBLER: I also don't know what to do with that piece of information. If that were, in fact, the case then I think it would require the sort of monitoring and data collection that would probably only happen in Class III and, yet, the published studies thus far--I can't comment, obviously, on their statistical validity. They are somewhat small but they didn't indicate that sort of a problem so I wasn't prepared for that.

DR. MCCAULEY: Exactly.

DR. DUBLER: Therefore, based on the studies that were here, it seemed to me that the descriptive information would be relatively easy to compile and prepare; now I am a little uncertain.

DR. WHALEN: Dr. Choti??

DR. CHOTI: I agree. I was kind of expecting this to be fairly straightforward but if it is really a topical application of an agent that really has a direct impact on the local tissue, then it muddies the water a little bit. But simply

based on the track record that these have been safe and the reactions have been very minimal, I think that the clinical safety data presented is quite good. I think there is little clinical evidence to suggest that there is any untoward effect of this material and, therefore, I am not sure that the Class III classification is warranted.

DR. WHALEN: Dr. Newburger?

DR. NEWBURGER: I concur with Dr. McCauley's assessment about the need to clarify the mechanism of action. Historically what we know about this type of dressing, I would agree with Dr. Choti.

DR. WHALEN: Dr. Miller?

DR. MILLER: Yes, I agree with all the comments that have been made. I wonder, can we invite our discussant back to the podium?

DR. WHALEN: The panel is free to ask anyone a question that they wish.

DR. MILLER: Could Dr. Fallon come back up because I too have been unaware of data which shows there is a leaching of silicone into the wound that is speculated to be the cause of the effect that we see.

MR. FALLON: It is study number nine in

the packet.

DR. MILLER: Who is the author of that one?/

MR. FALLON: That was Shigeki, Nobuoka. It is a study done in Japan, published in Skin Pharmacology Applied Skin Physiology.

MS. BROWN: I would like to ask a question. Is this study relevant to silicone sheeting or silicone gels?

MR. FALLON: Silicone sheeting, and we believe the distinction between the sheeting and the gel sheetings and the ointments is the release of silicon, not silicone, from the sheetings. It is hydrolyzed and these layers of silicone are released.

I also have a study that shows all the other proposed mechanism of actions have pretty much been disproved. I really can't give it out but it was done at Northwestern University by Dr. Mustow.

DR. WHALEN: I am just perusing this for the very first time, but it seems to me that these are mostly in vitro skin specimens--

MR. FALLON: Yes.

DR. WHALEN: --where they are looking at

the distribution simply locally in a piece of skin.

MR. FALLON: Yes.

DR. WHALEN: It is not like they put this somewhere in the groin and they--

MR. FALLON: Yes, correct, in vitro study, yes.

DR. WHALEN: So, I am having a hard time, again from first blush rapidly absorbing this, saying that there is documentation of absorption and systemic redistribution of silicone by this. There is nothing in here that states that to me.

MR. FALLON: Yes, I was very surprised when I saw that too. In reconsidering it with the mechanism of action, as it is known, these scars mostly happen to people that are from the tropics and the CD36 has been connected to the prevention of malaria and an antigen could have come--well, I wasn't prepared for this, but I can prepare--

DR. WHALEN: Well, let me ask you a more focused question. It is perhaps a slightly touchy area. I would think from your particular vantage point that you would not want to demonstrate that this is systemically absorbed. Am I correct there?

[Laughter]

MR. FALLON: Yes, I am just presenting

what appears to be happening. I don't know, I mean, I know I have a duty to my company, I own my company but I am just presenting and I know it is not helping and, you know, that is what it is. I am presenting to the board what our findings are and what we think.

DR. WHALEN: Are there any other questions? Dr. Doyle?

DR. DOYLE: If we have something that has been on the market this long with no untoward effects, is it necessary that we know the mode of action before we can approve it for classification?

DR. WHALEN: This is akin to the question I asked Dr. McCauley a short time ago, and there are certainly two answers to that question. There is long-term demonstrated efficacy and, yet--it may not be a related example--if we look at the explosion of latex allergy, I am sure twenty years ago people would have said there is millions and millions of use of latex without too much of a problem. So, without putting words in Dr. McCauley's mouth, I think he is suggesting that if, indeed, this is being now proposed as an effect we certainly can't ignore it, and I would agree with him. But I personally, from the perusal of this

letter, don't think that what we earlier had suggested to us has been demonstrated by this particular investigation.

MR. FALLON: And also, the study we did, the ten-year old Cica-Care did not throw off any of the silicon particles and that needs to be investigated. It is thought that silicone becomes toxic.

DR. WHALEN: Are there other questions for Mr. Fallon?

DR. MILLER: I just have one more. Based upon what you are telling us and what you have learned, your recommendation remains that we classify this as a Class I device?

MR. FALLON: Yes, on hypertrophic and keloid scars, yes. Yes, definitely. I mean, I don't see any safety issue. You could call Dr. Brawer. His number is right there. He is an expert. He is fairly articulate and you can ask him directly. He is more of an expert than I am.

DR. WHALEN: Dr. Dubler?

DR. DUBLER: Therefore, you have no other data but for the article that is numbered 9 that would demonstrate any danger from use on scar tissue?

MR. FALLON: Yes. No, I don't have any other data, no.

DR. DUBLER: So, if article number 9 is extinguished, then we are--

DR. MILLER: Yes, it also supports the fact that this should be used only on intact wounds.

DR. CHOTI: Although we still don't know the mechanism of action.

MR. FALLON: That is the proposed mechanism of action.

DR. CHOTI: Well, I think there is hydration, there is temperature, there are other modes of action. The real answer is whether you discount this article or not, we don't know how this works.

MR. FALLON: Yes.

DR. WHALEN: Thank you, sir. I think we are getting around to Dr. Chang.

DR. CHANG: I would use that same analogy of latex gloves, long history of use, relative safety, low percentage of side effects although there has been in certain populations, such as those with spinal cord injury meningomyelocele, certain increased risk for development of latex

allergies. So, that is not to say that with increasing use of silicone gel products individuals having this type of reaction may come forth. So, I would use that analogy to say, yes, there remains the potential, particularly if there is shedding or potential for absorption of silicone products with long-term use, that we may see this increasing prevalence.

But I believe, looking at the data presented by both FDA and industry, that there has been a long record of relative safety in the face of efficacy for this product. So, I would emphasize that it is intended for intact, closed skin and that it should be put into Class I.

DR. WHALEN: We haven't heard the words t-test today. Dr. DeMets, any comments?

DR. DEMETS: I just want to second what Dr. McCauley said. When I looked at the articles that were in our tab, I was struck by sort of two things. One, these studies are small and, therefore, whatever the effectiveness is, is going to be determined somewhat imprecisely, and some of them were uncontrolled and those that were controlled have a lot of missing data. So, I was less than overwhelmed with the benefit side of the

equation. Because these were small, I was sort of pondering the side effect side because if it is a low but serious event the number of patients in these studies would be way too small to detect that.

Now, maybe there are registries or the FDA database that could address that, but based on that literature I reviewed, I did see that we have enough numbers of patients exposed to really say too much about the safety. I am coming to this totally cold but that is just what I reflected when I read it.

DR. WHALEN: Ms. Brown?

MS. BROWN: I would support the Class I classification. As I understand, these have been regulated under 510(k)s since 1976. Is that correct, David?

DR. KRAUSE: They are considered pre-amendments. So, they have been around since before 1976. I don't think we had our first 510(k) for them until sometime in the '80's but they were, you know, identified as a pre-amendments device by that submission.

MS. BROWN: But it sounds like there has been a fair history of marketing with the product,

and there is a medical device reporting mechanism so if there are problems they do get reported to FDA. And, from what Sam Arepalli said, it sounds like there have only been two. So, it sounds like the risk is very minimal.

DR. WHALEN: Dr. Doyle, anything further on the first question? No? All right, the second question then that Dr. Arepalli has posed to the panel is still projected. Please discuss the risk of possible adverse skin reaction due to lack of biocompatibility for the scar management device and identify any other risks to health for these devices. Dr. Dubler, any thoughts?

DR. DUBLER: I have one question about the devices we haven't talked about thus far, which is they aid in the resolution of certain complex or difficult scar tissue. Would that scar tissue heal on its own over time, or does this do something that will create a different outcome?

DR. WHALEN: Yes, there might be multiple answers but I think the answer is yes to your question, both because it can both expedite and change outcome. But the primary beneficial effect, I think, has been to ameliorate the degree of hypertrophy within the scarring process so outcome

would be changed. Any of the plastic surgeons like to have another opinion on that?

DR. DUBLER: Since there can be a beneficial outcome which would not occur but for the use of this, and since there doesn't appear to be any documented negative reaction but for two cases, and since I don't know what to do with article number 9, it seems there are no serious adverse health reactions that would argue against classifying as a Class I.

DR. WHALEN: Dr. Choti?

DR. CHOTI: I agree.

DR. WHALEN: Dr. Newburger?

DR. NEWBURGER: I agree as well.

DR. WHALEN: Dr. Miller?

DR. MILLER: I agree.

DR. WHALEN: We are on a concise streak. Dr. Chang?

DR. CHANG: I agree. The caveat is in the usage. In one of the two examples a patient had the product on for over 30 hours. So, I believe that in labeling patient education has to be very important to limit to to 12 hours, I believe, the consecutive hours that this product should be applied to try to decrease the amount of skin rash

as a result of excessive moisture from overuse of the product. But, otherwise, I agree that this should be a Class I product.

DR. WHALEN: Dr. DeMets?

DR. DEMETS: I agree with the previous comments.

DR. WHALEN: Ms. Brown?

MS. BROWN: I agree with the previous comments.

DR. WHALEN: Dr. Doyle?

DR. DOYLE: I agree.

DR. WHALEN: And, Dr. McCauley?

DR. MCCAULEY: Same, I agree.

DR. WHALEN: Now that the panel has discussed the FDA questions and our deliberations seem complete, we have time for any final remarks. Dr. Arepalli, is there any final comment from FDA, or anyone else on behalf of FDA?

DR. WITTEN: I just want to clarify that the second question was to discuss or identify any other risks that you all see. I think some were noted and if those are all the risks, that is fine but I just wonder if there are any other risks that haven't been discussed that anybody wants to comment on.

DR. WHALEN: I think we have hit them. Is there any final comment from anyone in the silicone elastomer for scar management industry? If so, would you please raise your hand? Yes, sir? Would you please again, even though you have spoken to us before, give your name and affiliation and any financial interest in the devices being discussed?

MR. DILLON: I am Mark Dillon. I am the president of Bio Med Sciences and, obviously, I have a financial interest in the company.

I have a couple of comments. One is that I am aware of one paper that was done by Dr. William Monofeld where he looked for traces of silicon metal in skin biopsies taken, and I believe from a control source as well, underneath the treated area. If I recall correctly, he saw a fairly high baseline content of silicon metal in the skin which he concluded could be from a number of different sources--the fact that silicone is often coated on capsules to make them easier to swallow and on hypodermic needles and so forth--and he concluded that there was no increased amount of silicon in the skin treated with silicone sheeting. So, I thought I would share that with the panel.

I would strongly agree with the idea of

not indicating this product for use on open wounds. For one, the obvious reason is it is unknown and there is a classification for that already. Secondly, these products are always reusable and after the first application they are no longer sterile, even if they were provided sterile and most of them are not. So, I think with strong labeling to indicate against use on open wounds, that issue would be largely put to rest.

I would be willing to share a theory on mechanism of action if the panel would like to hear some of my experience. I have noticed clinically that with the use of these products on hypertrophic scars, particularly in contractures over a joint, you can see a benefit in range of motion occur with a period of hours of use. To me, this is an indicator that there is a hydration mechanism and that this effect will reverse itself if the use is discontinued.

Secondarily, we see over a longer period of time a remodeling of the scar, which may or may not be due to hydration, but that second effect is what is more permanent. DR. WHALEN: Thank you, Mr. Dillon.

MR. DILLON: Thank you.

DR. WHALEN: Mr. Fallon, do you have any final remarks?

MR. FALLON: The trace of silicon in *in vivo* models will probably not come up because it is the job of the CD36 and scavenger cells to take those away. So, I really can't see how one could set up an experiment, besides *in vitro*, to show that it is getting into the skin. So, I just wanted to clarify that.

Classification Questionnaire and Vote

DR. WHALEN: Thank you. Now we will complete the classification questionnaire and supplemental data sheet. Ms. Marjorie Shulman, in the Office of Device Evaluation Classification, Reclassification, will assist us as we go along. After the formal panel discussion of each question we will note the answers for each blank on the data sheet as Ms. Shulman reads them out, and she will record it on the overhead for all of us to see. The voting members of the panel will vote then on the completed questionnaire and supplemental data sheet and this will then constitute the panel's recommendation to the FDA. Procedurally, are there any questions on what we are about to do next?

[No response]

MS. SHULMAN: Are we ready? the first part on the sheet is just your panel name and you can fill that out. That is administrative, and the date; the generic type of device.

Then the first question, is the device life-sustaining or life-supporting?

DR. WHALEN: We can just go around the table, and this is for voting members. So, we can start on this first question, please, with Dr. McCauley.

DR. MCCAULEY: The answer to the first question would be no.

DR. DUBLER: The answer to the first question is no.

DR. CHOTI: No.

DR. NEWBURGER: No.

DR. CHANG: No.

DR. DEMETS: No.

MS. SHULMAN: The first one is no. Is the device for use which is of substantial importance in preventing impairment of human health?

DR. WHALEN: Just to stagger the way we answer them, Dr. Dubler?

DR. DUBLER: No.

DR. CHOTI: No.

DR. NEWBURGER: No.

DR. CHANG: No.

DR. DEMETS: No.

DR. MILLER: No.

MS. SHULMAN: The second one is no. Number three, does the device present a potential unreasonable risk of illness or injury?

DR. WHALEN: Dr. Choti?

DR. CHOTI: No.

DR. WHALEN: Dr. Newburger?

DR. NEWBURGER: No.

DR. CHANG: No.

DR. DEMETS: No.

DR. MILLER: No.

DR. MCCAULEY: No.

DR. DUBLER: No.

MS. SHULMAN: The third one is no. We now go to number four, did you answer yes to any of the above three questions? That answer is no.

Then we go to number five, is there sufficient information to determine that general controls are sufficient to provide reasonable assurance of safety and effectiveness?

DR. WHALEN: Starting with Dr. Newburger?

DR. NEWBURGER: Yes.

DR. MILLER: Yes.

DR. CHANG: Yes.

DR. WHALEN: Dr. DeMets?

DR. DEMETS: I will vote no.

DR. WHALEN: Dr. McCauley?

DR. MCCAULEY: Yes.

DR. DUBLER: Yes.

DR. CHOTI: Yes.

MS. SHULMAN: The answer to that one is yes. On your sheets, you may mark whatever you voted yourself. So, if the answer to that is yes, it is classified into Class I.

So, we can skip two. We actually get to skip all the way to the second page because all the rest of the questions apply to Class II or Class III devices.

Question 11 is a prescription question. Can there otherwise be reasonable assurance of its safety and effectiveness without restrictions on its sale, distribution or use because of any potentiality for harmful effect or collateral measures necessary for the device? If you answer yes, you are saying it is not a prescription device. If you answer no, you are saying it is a prescription device.

DR. WHALEN: Beginning with Dr. Miller.

DR. MILLER: No.

DR. CHANG: Yes.

DR. MILLER: No means that it requires a prescription, right?

DR. WHALEN: Just re-explain, please.

MS. SHULMAN: The question is backwards. If you answer yes, it is not a prescription device. If you answer no, it is a prescription device.

DR. WHALEN: Do you still wish, Dr. Miller, to vote no?

DR. MILLER: Yes, no, I mean--

[Laughter]

--I feel it should be a prescription device.

DR. WHALEN: That is a no. Are you still yes, Dr. Chang? Dr. DeMets?

DR. DEMETS: I will be a no.

DR. WHALEN: Dr. McCauley?

DR. MCCAULEY: Prescription device, so that makes it a no.

DR. WHALEN: Dr. Dubler?

DR. DUBLER: Are we allowed to talk among ourselves?

DR. WHALEN: Sure.

DR. DUBLER: In other words, do you think it would be important for a physician to know that this use was taking place and to direct and supervise its use?

DR. WHALEN: Well, there are individual state laws, if I can interject, that regulate who can write prescriptions, and there are certainly many places in the United States now where prescriptions can be independently written by non-physicians, but it would be by a licensed practitioner.

DR. DUBLER: So, someone should be aware of the use and supervise the use who has specialized medical knowledge.

DR. WHALEN: Correct.

DR. DUBLER: I agree. So, that should be a no.

DR. WHALEN: If you agree with that practice, yes.

DR. DUBLER: Okay. No.

DR. WHALEN: Dr. Choti?

DR. CHOTI: No.

DR. WHALEN: Dr. Newburger?

DR. NEWBURGER: No.

MS. SHULMAN: The answer to that is no so

we go to 11(b), identify the needed restrictions for the device. The first one is only upon the written or oral authorization of a practitioner licensed by law to administer or use the device. The second, to use only by persons with specific training or experience in it. Third, to use only in a certain facility. Or, you could come up with any other.

DR. WHALEN: Among those choices, Dr. Chang, what would you suggest?

DR. CHANG: Well, in the State of Iowa it is available in drug stores without prescription. To me, I will just repeat what I had said as an aside, it is about 70 percent effective overall, looking at the literature. It has low danger provided the label says to not wear it more than 12 hours; to discontinue it if there is a skin rash; and it is helpful but kind of a very fancy bandage over intact skin. So, I don't believe a prescription is necessary. It is available already in my state.

DR. WHALEN: So, you wouldn't want to check any of these off?

DR. CHOTI: I don't think it is indicated.

DR. WHALEN: Fair enough. Dr. DeMets?

DR. DEMETS: I am going to stick with my colleague.

DR. WHALEN: Dr. McCauley?

DR. MCCAULEY: Since I voted no, I would say that only upon the written or oral authorization of a practitioner licensed by law to administer these. From my interpretation of this, this is the least restrictive of the three that we have, is that not correct?

MS. SHULMAN: Yes, that is correct.

DR. DUBLER: I want to come back to Dr. Chang because I think I might have voted differently on 11(a) if I had heard your comment before I voted.

DR. CHANG: That it is available?

DR. DUBLER: It is available in Iowa over-the-counter, and there have been no reports of excessive use reactions. I mean, there is nothing negative in the literature.

DR. CHANG: Aside from the two.

DR. DUBLER: Aside from those two, right. Do we know if it is available in the same way in other states? It is?

DR. WHALEN: Can I just ask in that regard though, since we know that adverse events are

grossly under-reported by physicians, number one, what mechanism exists for the lay public on OTCs--

DR. CHANG: To see a physician because of a rash.

DR. WHALEN: But they may just have rashes and not be doing anything about it, other than stop using it and seeing if the rash goes away.

DR. CHANG: And it should go away.

DR. MILLER: Can I make a comment? I mean, I think the goal of this is to treat the scar and this is a tool to treat the scar. I think that, you know, a physician needs to evaluate the patient and decide on how to treat the scar. For people just to go on their own and select this, I think it doesn't make as much sense to me because they may be selecting it for the wrong types of scars, the wrong types of problems, and I think it should be guided by a physician.

DR. WHALEN: Getting back to going around the table, Dr. Dubler?

DR. DUBLER: Yes, I find this puzzling because if we lived in a nation where everybody had access to physicians or nurse practitioners or other people who could manage their care, then I would tip in one direction. But since some 42

million people don't and so requiring a prescription will, in fact, be a barrier to access for something that could be helpful in the long run, I would like to change my vote on 11(a) to a yes and, therefore, I don't need to choose anything from 11(b). Correct?

DR. WHALEN: I think that is perfectly acceptable. That would make the vote still 5-2 in favor of no in question 11, unless there is anyone else who wishes to reconsider.

MS. BROWN: Could I ask a question? If the panel votes that this needs a prescription, is the State of Iowa now going to have to take it off the over-the-counter mechanism of distributing the product?

DR. WHALEN: Dr. Witten?

DR. WITTEN: I am not sure what the State of Iowa would do, but if we make it a prescription use, then they have to interpret what that means.

DR. WHALEN: Keeping in mind that we are an advisory panel and our advice is going to the FDA to deal with this as they see fit, again, on question number 11, is there anyone else who voted in either direction and wishes to change their vote?

[No response]

Dr. Choti, which among the options in 11(b) would you choose?

DR. CHOTI: I would say that written or oral authorization is warranted in this situation, the first one.

DR. WHALEN: The first? Very good. Dr. Newburger?

DR. NEWBURGER: Also written or oral authorization of a practitioner.

DR. WHALEN: Dr. Miller?

DR. MILLER: I agree, written and oral authorization.

MS. SHULMAN: That is it for the general device questionnaire. We will move on to the supplemental data sheet. The first question for your sheet, the generic type of device we have covered that. You can just write that in. The advisory panel is surgery, General and Plastic Surgery.

Number three, is the device an implant? No. The indications for use, here we won't have to rewrite it if everybody agrees to the indication that was presented during the meeting earlier.

DR. WHALEN: This indication was one that

had the wording in it about uncompromised skin. So, is there anyone who wishes to modify that in any way?

DR. DUBLER: I thought Dr. McCauley--

DR. MCCAULEY: I would like to modify it and say intact hyperproliferative scar disorders, which includes keloids and hypertrophic scars.

DR. WHALEN: Is there consensus on that wording?

DR. CHANG: To clarify, would that be not using for the control of hypertrophic and keloid scar--I mean, if we have both the words hypertrophic and keloid scar and then put in the words for intact hyperproliferative skin disorder, then we have it duplicated.

DR. MCCAULEY: I think the way it reads is for intact or uncompromised skin for scar control. Is that not correct?

DR. WHALEN: Scar management.

DR. MCCAULEY: Or scar management.

DR. WHALEN: Scar management device is a silicone sheeting product intended for use on uncompromised skin for scar management.

DR. MCCAULEY: Yes, for scar management. So, intact--

DR. CHANG: And for proliferative---

DR. MCCAULEY: Scar disorders. Then in parentheses you can put hypertrophic scar and keloids. But I think the key basically is to encompass both of them and make sure that you use them for intact.

DR. CHANG: I agree as proposed.

DR. MILLER: Instead of intact could we say epithelialized wounds or closed wounds? I just happen to like epithelialized wounds, it is more specific to me.

DR. MCCAULEY: I have no objection.

DR. CHANG: I would vote for keeping it simple, and if you want to be explicit about intact I would vote to say closed, intact.

DR. MILLER: I like that, closed, intact.

DR. WHALEN: Closed intact? Technically, we would almost have to have a biopsy to definitively declare that it is epithelialized.

DR. CHOTI: Well, the distinction is perhaps a fresh incision and it may be semantics as to whether it is a closed wound or not but, clearly, it is not to be applied on a freshly closed incision.

DR. MCCAULEY: What you are saying is that

it has to be a hyperproliferative problem.

DR. CHOTI: Yes, I think that just replacing the word "uncompromised" with "intact" is sufficient, and leave it just for scar management without specifying hyperproliferative state.

DR. WHALEN: The only problem with healed, as you plastic surgeons know better than I, you can make an argument for a year that it is not entirely healed.

DR. MILLER: That is true.

DR. WHALEN: Even though it is totally epithelialized.

DR. MILLER: That is correct; that is true.

DR. WHALEN: So, where are we?

DR. CHANG: Back to intact.

DR. MCCAULEY: Hyperproliferative scars.

DR. CHANG: Yes.

DR. WHALEN: So, intact skin for management of hyperproliferative scars?

DR. MILLER: Right.

DR. WHALEN: Is that the way we are doing it?

DR. CHANG: Intact skin with hyperproliferative scars, parentheses, hypertrophic

or keloid.

DR. WHALEN: Okay.

DR. AREPALLI: Are you going to stick with "management of?"

DR. WHALEN: No, I don't think "management of," Sam. I didn't hear that. The word management is the third word, the scar management device is a silicone sheeting product intended for use on intact hyperproliferative scars, parentheses for keloids and hypertrophic scars.

DR. NEWBURGER: Question.

DR. WHALEN: Yes, ma'am?

DR. NEWBURGER: Is not one of the intents of these dressings to be used in an area where you strongly feel that there is going to be a keloid? Can't you use that on a preventative basis? I thought that was some of the information that we got, if you have an incision that is, you know, in this triangle and you have someone who characteristically forms keloids, wouldn't you want to use this as soon as the area has epithelialized, Dr. McCauley?

DR. MCCAULEY: There was one study in our packet that actually dealt with that issue. You all may know better than I, but I didn't feel that

it really had a lot of good data, but what they did suggest was that maybe in areas which are prone to the development of hypertrophic scars it may be useful in terms of prevention, but there was just one paper.

DR. WHALEN: Phyllis?

DR. CHANG: I would be content to leave that as an off-the-shelf use.

DR. WHALEN: All right.

MS. SHULMAN: So we agree upon the wording. Number five, the identification of any risks to health presented by the device. We can say as covered in the panel meeting or anyone can add anything they wanted to.

DR. WHALEN: Agreeable to say as covered in the panel meeting? All right.

MS. SHULMAN: Number six, the recommended advisory panel classification and priority--we only need a classification, which is Class I, and the priority we only need for Class II or three.

Number seven, if device is an implant or is life-sustaining or life-supporting and has been classified in a category other than III, explain fully the reasons. We can skip this.

Number eight, the summary of information

including clinical experience or judgment upon which a classification recommendation is based. If you wish, we could put in there what was covered in the panel meeting as a summary for the reasons.

DR. WHALEN: Seeing no objections, we will do that.

MS. SHULMAN: Number nine, the identification of any needed restrictions on use of the device. That is a prescription question again. We can just refer to question 11(a) of the general device questionnaire.

Number ten, if the device is in Class I, recommend whether FDA should exempt it from registration and listing, premarket notification, records and reports and good manufacturing practices. It can be all, any or none.

DR. WHALEN: I may have lost our order track but I think Dr. McCauley, if we could start with you on this?

DR. MCCAULEY: Shall I go through each one individually?

DR. WHALEN: Or any of those that you wish to say it should be exempted from.

DR. MCCAULEY: None.

DR. WHALEN: Dr. Dubler?

DR. DUBLER: Then I don't understand the question. I would assume, given Class I, we would want to exempt it from (a) and (b). Doesn't that follow from Class I?

MS. SHULMAN: Well, registration is where you register your manufacturing facility and listing is where you list the device. Number two is premarket notification. Most Class I devices are exempt from premarket notification, however, there are about 53 reserved Class I so they do require 510(k)s to come in even though they are Class I.

DR. MCCAULEY: Can I ask for discussion, particularly from Dr. DeMets? In your review of the statistical data, what is your opinion in terms of efficacy based on the data that you were presented?

DR. DEMETS: Well, only what was in our packet because that is all I know. The studies were small. Some of them were uncontrolled. Some of them, even though they had controls, had substantially missing data or patients were excluded from the analysis which leaves it open to some potential to bias. So, I am not saying it was not effective, I am just saying I am not sure how

effective it is based on the data that was presented. There are pretty small numbers and, you know, by good clinical trial design these are not particularly strong studies. So, my earlier remarks were not on the safety part so much as on the efficacy part.

DR. WHALEN: Does that answer it for you?

DR. MCCAULEY: Yes, well, if I can get some clarification again on registration and device listing?

MS. SHULMAN: Registration is a paper format where people send into our Office of Compliance where their manufacturing facility is located. Listing is where they list what devices they are making, and that is for inspectional purposes.

DR. MCCAULEY: Is that not part of GMP or is that a separate issue?

MS. SHULMAN: It is separate. Few devices are exempt from registration and listing, but there can be some that are.

DR. DUBLER: And what does C mean, records and reports?

MS. SHULMAN: That is another compliance issue on their record keeping. Everyone has to

keep records, but the manner in which they do it, would they have to follow our rules, the rules they would follow under the GMPs, the good manufacturing practices.

DR. DUBLER: So, we have had two reports of adverse reactions. If there were other such reports I would want them to come forward. If I check any of these things, A, B, C and D, does it prevent that adverse reporting or does it discourage it?

MS. SHULMAN: No, I don't believe it does.

DR. MCCAULEY: It means they are not required to report them.

MS. SHULMAN: I am sorry, I misunderstood, yes, they would not be required to report.

DR. DUBLER: So, the first one just means they have to tell us where they are.

MS. SHULMAN: They have to tell us where they are and list what devices they are making in that facility.

DR. WHALEN: All right.

DR. CHANG: And, could you clarify again what is item B? What does that mean?

MS. SHULMAN: The second one is premarket notification, also known as 510(k). So, if it is

exempt from that they can go to market without coming in and getting a clearance from us.

DR. DUBLER: But they are already on market.

DR. WITTEN: A sponsor with a new device, if somebody comes in with a new device, if they want to market and they need to submit a premarket notification, that means they send a premarket notification to us to review before they go to market. If they are exempt from premarket notification and, as Marjorie Shulman already mentioned, most Class I devices are but there are some that are reserved, then, if they are exempt, they don't need to send an application. If they are not exempt they need a specific clearance from us prior to going to market.

DR. MCCAULEY: As I recall, each of the industry representatives recommended Class I with a 510(k). Is that not correct?

DR. WHALEN: They did. With no offense to our industry representatives, they certainly would have an interest in so recommending. Any industry representative would have it in their own best interest to put up a potential wall for competitors entering the marketplace. That is not to say that

their intent is not noble and scientifically founded. Are we clear on what we are talking about in this question? Dr. McCauley?

DR. MCCAULEY: I think I will stick with my original vote for no exemption.

DR. WHALEN: And Dr. Dubler, will you still go with A or B?

DR. DUBLER: I would exempt B but not the others.

DR. WHALEN: Solely B, but you would not vote for A?

DR. DUBLER: Solely B.

DR. WHALEN: Dr. Choti?

DR. CHOTI: I think I would not exempt any of them.

DR. WHALEN: Dr. Newburger?

DR. NEWBURGER: No exemption.

DR. WHALEN: Dr. Miller?

DR. MILLER: No exemptions.

DR. WHALEN: Dr. Chang?

DR. CHANG: No exemptions.

DR. WHALEN: Dr. DeMets?

DR. DEMETS: No exemptions.

MS. SHULMAN: Then number 11, if there are any existing standards to the device assemblies, components, device materials or parts or

accessories that you know of that you would like us to apply to these devices, then this is where you can list them.

DR. WHALEN: I don't know that we need to go around for this. Is there anyone who wishes to stipulate such? I see none.

MS. SHULMAN: Then that is the end of the sheet. You go around once and vote for these sheets to be voted on as discussed as a Class I reserve device, requiring 510(k).

DR. WHALEN: So, in effect then, we are asking for a motion to accept the classification worksheet as filled out, with a recommendation for Class I silicone elastomer for scar management intended for use on intact skin, hyperproliferative scars, parentheses, keloid and hypertrophic scars. Is there a motion to that effect?

DR. CHANG: So moved.

DR. WHALEN: Is there a second?

DR. CHOTI: Second.

DR. WHALEN: It has been moved and seconded that silicone elastomer for scar management intended for use in intact skin hyperproliferative disorders, parentheses, keloid and hypertrophic scars, be classified into Class I.

All those in favor, voting members signify by raising their hands, please.

[Show of hands]

All of those opposed? Dr. Dubler abstains. So, it is six yes, one abstention.

DR. DUBLER: Can I take just one minute, Dr. Whalen?

DR. WHALEN: You certainly can because each member has to take, maybe not one minute but ten to fifteen seconds to explain why they have voted in the way that they did. If we could start with Dr. DeMets?

DR. DEMETS: I am not sure I can explain. Well, I think that we have discussed the issues and I can accept what we voted earlier.

DR. WHALEN: Dr. Chang?

DR. CHANG: My comment is that the science is soft, as previously mentioned, but for some this is efficacious. The track record over many years is that it is a safe product. Side effects can be prevented if it is used correctly. I would compare use of nonsteroidal anti-inflammatories. They can have serious side effects but they have become in common use relatively safe. They can cause ulcers but they are available over-the-counter and the

price has gone way down. So, if this is a useful product, very safe, with many individuals having the hyperproliferative scars, you know, I voted to have it as a non-prescription Class I device.

DR. WHALEN: Dr. Miller?

DR. MILLER: I think it is a very practical device that certainly appears safe. Although we don't understand exactly why it works, I don't think that should prevent us from making it available.

DR. WHALEN: Dr. Newburger?

DR. NEWBURGER: I think this is a very useful device. It has been very effective for many people. By making it a prescription Class I device I think we have the potential for avoiding a lot more side effects, and I feel there are many more than certainly have been reported. I think this gives more safety to the community.

DR. WHALEN: Dr. Choti?

DR. CHOTI: I agree with the comments. I think it sounds like this device is already being used a lot. It sounds like it is safe and it probably is effective. I think we are all a little bit frustrated by the fact that we don't know how it works; that we don't really have a lot of

records of its application. So, what can be done by industry, academics and others to study a little bit more the mechanisms and registry, and I think we have voted, or I have voted in a way to, best as we can, encourage some kind of additional record keeping. But I think it sounds like it potentially has a clinical role so that is how we voted.

DR. WHALEN: Dr. Dubler?

DR. DUBLER: I abstained for a very particular purpose. I think that the panel's discussion was very thoughtful but indicated to me that this was, when used correctly for the right indications, a safe application that could have a real effect on someone's quality of life and on the outcome of the resolution of these scars. I work in the Bronx. We have a lot of people who don't have health insurance, and when they have a problem and they can deal with it over-the-counter they have a chance of helping themselves. When they have to go through a licensed practitioner they don't get that help. A lot of kids have these scars, a lot of mobility problems.

I abstained because I think we should not have voted this to be a prescription item. I think the single greatest ethical problem in American

medicine is access to care, and we have just put up a barrier to what may be safe and helpful.

DR. WHALEN: If I can parenthetically add, it is perhaps only fair, if I have in any way impugned manufacturers in putting up 510(k) restrictions, to state that physicians putting up prescription barriers is probably not the most disinterested party to do so.

DR. DUBLER: Here, here.

DR. WHALEN: Dr. McCauley?

DR. MCCAULEY: I think the device is safe. I think that it probably is efficacious. I think the data is somewhat soft, and I think the way we voted probably will lend itself to really determining how efficacious this product really is.

DR. WHALEN: Though not voting, any comments, Dr. Doyle?

DR. DOYLE: I feel very strongly as Dr. Dubler does since it is considered safe and has been shown efficacious, or has not been shown not to be efficacious, why are we limiting people's access to it?

DR. WHALEN: Ms. Brown:

MS. BROWN: I have the same question about access. If it is available currently

over-the-counter, it seems like we may have put up another barrier to its use that wasn't here before the panel meeting.

DR. WHALEN: Thank you. I would like to announce that the recommendation of the panel, with six votes for the motion and one abstention, is that the silicone elastomer for scar management intended for use in the management of intact skin--which I still won't get right but what you see up on the screen, with hyperproliferative scars, parentheses, keloid and hypertrophic scars, be classified into Class I.

In so doing, I would like to thank the panel and thank Dr. Arepalli and the industry reps for what they have done for us. We have another item of business but we will take a ten-minute break and reconvene promptly at 3:25 to being that process.

[Brief recess]

Reclassification of Absorbable Hemostatic Agents and Dressings

DR. WHALEN: I would like to call this meeting back to order. Could I first ask that the voting panel members pass toward the center of the table, toward me, their classification

questionnaires on the last item of business so that we can collect them for the FDA?

I would like to remind the public again that while this portion of the meeting is open for the public for their observation, public attendees may not participate except at the specific request of the panel.

We now will proceed to the open committee discussion. We will begin the discussion on the reclassification of absorbable hemostatic agents and dressings with serial presentations from industry, first by Dr. John D. Paulson, vice president for quality assurance and regulatory affairs, Johnson & Johnson Wound Management, a Division of Ethicon, Inc., followed by Ms. Ronnemoes Bobak, vice president for product development, Ferrosan A/S, and then Ms. Judith E. O'Grady, senior vice president, regulatory, quality and clinical affairs, Integra LifeSciences Corporation.

The FDA presentation and a reading of the FDA questions will follow these presentations. We will then have a general panel discussion of this topic, followed by a more focused panel discussion aimed at answering FDA's questions. Before we

complete the reclassification worksheet and supplemental worksheet, we will have an open public comment period. Then we will complete the reclassification worksheet and supplemental worksheet. The vote on these worksheets will constitute the panel's recommendation to the FDA.

I would like to remind public observers at this meeting that while this portion of the meeting is open for public observation, again, public attendees may not participate except at the specific request of the panel. I probably should seriously point out that even though I am from Robert Wood Johnson Medical School in New Brunswick, New Jersey, there is not a financial interrelationship with Johnson & Johnson although, God knows, my dean would love to have a stronger one. We will begin with Dr. Paulson's presentation.

Industry Presentation

DR. PAULSON: Dr. Whalen, Dr. Krause, Dr. Witten and panel, thank you for the opportunity to present here today.

There are several different types of products in the category of absorbable hemostatic agents. I am here today to present concerning

Surgicel, oxidized regenerated cellulose, representing one of these product types.

I would like to talk to you about globally available ORC products while noting that Surgicel is currently the only available ORC product in the United States. There was previously another manufacturer making a similar product, using essentially the same chemistry and manufacturing process which we licensed jointly from the third-party company. They have since stopped making that product. But their safety record is going to be discussed, I am sure, by Dr. Krause and will reflect product made by the same manufacturing process in essence.

I will talk to you briefly about the manufacturing process; the mechanisms of hemostasis, just very briefly; biocompatibility and hemostasis data; and then provide a brief summary of my conclusions. I will try to do that all in less than fifteen minutes.

The Surgicel family of absorbable hemostats includes three basic product types, Surgicel, Surgicel Nu-Knit and Surgicel Fibrillar, representing different physical forms of product made with essentially the same process, although

representing different weaves and manufacturing processes after the chemistry has taken place.

These products are used adjunctively in surgical procedures for the control of capillary, venous or small arterial bleeding and rapidly stop the bleeding by acting as a matrix for the formation of a clot, and some other mechanisms that I will talk to you about a little bit later. The product is often left behind in part of in whole and is readily absorbed from the site of implantation with minimal tissue reaction, which is very important because it is frequently used in cardiovascular procedures and frequently in neurosurgical procedures where other methods of hemostasis may not be suitable, for instance, electrocautery.

There are other ORC products available in the global market. This is Cellulostat. it is available in Taiwan and China. You can see it magnification at 12x having a slightly different pattern of knit or weave. And, there is an ORC product developed from Europe, by the name of Curacel. So, I will talk a bit about those products as well.

This is just to remind you that

regenerated cellulose products are more than just an isolation of cellulose. They are derived from wood pulp which contains about 50 percent cellulose by weight, and also contains significant amounts of lignin and other inter-fibrillar materials which act as adhesives to kind of keep the physical structure of the wood intact. There are significant chemical processes in place here that affect the qualities of the fabric which becomes the raw material for the oxidation process. This basically digests the cellulose and then reconstitutes it prior to oxidation. The material that we are talking about here is bright rayon, and it is essentially pure cellulose.

This then goes into knitting and purification processes and conditioning of the fabric, controlled oxidation reactions which are used to define chemistry and define processes, involve displacement of solvents and reactants, purification of the materials, dehydration and then processing the material into its final product forms, along with sterilization and QA testing and release.

What I wanted to call your attention to in all of this is really the complex nature of the

processing that is involved. This is not just an isolation of cellulose as a chemical derivation, and you can think of this as a biosynthetic material rather than an isolated biological material.

Cellulose is a polymer of glucose basically, and oxidized regenerated cellulose in its simplest form involves the oxidation at the sixth position, changing it from an alcohol function to a carboxylic acid function. There are also other chemical byproducts, and I will call your attention to the 2- and 3-ketone ORCs as well as aldehydes, ketones, dialdehydes, and so on. These can vary in ratios depending on the controls and nature of oxidants in the oxidation process.

Again, we are talking about cellulose-related materials. This is a reminder that cellulose itself does not absorb. This is a cotton suture that has been implanted for two years. You can see a chronic inflammatory reaction here and continued presence of the cellulose. Cellulose is also well-known to surgeons from use in gauze, and lint from gauze is well-known to cause chronic inflammatory reactions and adhesions. We don't want to end up with cellulose so

consistency of the process is important to achieve a biocompatible and degradable material.

This is just a brief reminder of the complex relationship between physiologic processes involved in hemostasis, involving vasoconstriction, platelet activation, coagulation activation, conversion of fibrinogen to fibrin by thrombin. I will mention briefly that Surgicel acts both in terms of platelet activation and activation of intrinsic and extrinsic pathways or coagulation activation.

Surgicel at the wound site has multiple mechanisms. Here it is applied to a vessel. There is fluid absorption which results in a relative hemoconcentration. There is hemoglobin oxidation resulting in a gel formation or false clot which helps achieve tamponade in conjunction with manual compression.

You can see in the upper right-hand depiction adherence of platelets to the fibrillar structure of the material and ultimately clot formation on the matrix of fabric.

I will use this swine spleen incision picture to demonstrate some of the actual use of the product. You can see here that in a model

which we used to measure hemostasis time, using a controlled incision of 1.5 cm by 0.3 cm deep, that you see a darkening of the blood which has to do with its oxidation. You can see gel formation and false clot formation, fluid absorption, and so on. In this model we applied digital compression and can measure time to hemostasis, as I mentioned earlier. I will refer to some data later from this model.

I am going to try to relate to you some of the mechanisms of action that we talked about earlier in hemostasis and some of the attributes of Surgicel. I will also talk to you about how they relate to controls which exist in the U.S. Pharmacopeia.

In the first column you will see mechanisms of action include tamponade due to digital compression, fluid absorption, swelling and gel formation. Then, at the chemical and biologic level we talked earlier about protein adsorption, platelet adherence, platelet aggregation and platelet activation, and intrinsic and extrinsic pathway activation. This relates to a variety of physical and surface chemistry attributes of the product that are shown in this panel. Then, if one

looks at USP specifications for oxidized regenerated cellulose, you see that they are very incomplete in addressing those items which we identify as important to achieving effectiveness of the product and in achieving hemostasis.

Similarly for biocompatibility, we have highlighted just a few of the key areas of biocompatibility that are important here--cytotoxicity, acute inflammation, biodegradation and absorption, immunogenicity and neurotoxicity.

Surgicel properties include carboxyl content and pH. Degradation, interestingly, does not appear to be related to carboxylation of the alcohol functions but, rather, the ketone formation at C2 and C3, which is not controlled by USP specifications or other recognized standards for these products.

In terms of immunogenicity and neurotoxicity, the exact determinants are not clear, but it is clear that they depend on high material purity and controlled chemical processes and ingredients. Again, USP specifications appear to be inadequate in addressing these essential requirements of the product.

We have done some physical and chemical analysis of the three product types that I showed you earlier. Many of these are USP tests, for instance, identification loss on drying, nitrogen content and carboxyl content are USP tests. You will see that Surgicel passes all of these, while Curacel fails for carboxyl content; Cellulostat fails on several accounts. In the right-hand column you can see those USP specifications for these parameters.

We have also assessed pH, which is somewhat related to carboxyl content but post-oxidation treatment can neutralize the pH and add back other ions. You can see that Cellulostat has a different pH, while Curacel appears to have calcium added into the process.

Physical strength varies which, of course, can affect clinical use. Water solubility varies for these products and spectral identification suggests that Cellulostat is not, in fact, ORC despite its labeled claim to be so.

Time to hemostasis was measured in the model that we showed you earlier. The top two bars represent some historical data that we have for Surgicel Nu-Knit and Surgicel. Then, due to

limited numbers of samples available for Curacel and Cellulostat in the short time since this meeting was announced, we have done some head-to-head comparisons of Cellulostat and Curacel, and you can see that with Surgicel the mean time to hemostasis for those specific wounds that we discussed earlier is approximately eight minutes; for Curacel, approximately ten minutes; and for Cellulostat, essentially none of them achieved hemostasis in the 12 minutes that we defined as the maximum time period for this model.

So, what do we conclude from all that? Our summaries are that Surgicel Absorbable Hemostat does, indeed, have a long history of safety and effectiveness. I think Dr. Krause will speak to you about that. Given the limited time for this presentation, I haven't gone into it but it certainly does have a commendable history.

There is complex chemistry and processing required to create the unique product properties here. There are multiple physiological interactions required for safety and effectiveness. Other ORC products are not equivalent, and USP requirements do not address many critical product attributes.

So, our conclusions are that the USP is not adequate to control key product attributes, and that we do not know of other standards for these products which are established and accepted.

Finally, in the absence of recognized standards, we believe that reclassification is not appropriate. I would again refer back to the fact that these products are often left as implantable devices in critical portions of the circulatory system and the central nervous system. So, I am sure that as physicians and scientists you can appreciate the great degree of control and assurance of biocompatibility and effectiveness that are needed there. Thank you.

DR. WHALEN: Questions for Dr. Paulson?

MS. BROWN: I have a question. If the FDA developed a guidance document would you be in support of a down-classification?

DR. PAULSON: I think if an adequate guidance document can be created and is dictated in the regulation, then that would be a reasonable approach. However, at this time I am not aware of what the contents of that would be so I would be reluctant to say that that is the way to go in the absence of a standard that we could ponder and

consider the adequacy of.

MS. BROWN: thank you.

DR. WHALEN: Other questions?

[N response]

Thank you. Next, we will hear from Ms. Bobak.

MS. BOBAK: First, I would like to thank you for giving me the opportunity to speak here, and having the ability to have an impact during this panel discussion on reclassification of absorbable hemostatic agents and dressings.

My name is Lone Ronnemoes Bobak. I am representing Ferrosan. Ferrosan is a Danish medical device manufacturing company, and we have given the distribution rights of our absorbable gelatin sponge Surgifoam to Ethicon and they distribute our absorbable gelatin sponges.

What I will be talking about is the current regulatory status because it is different in Europe and in U.S. I will talk about the essential quality control elements which we have implemented. I will talk about the usage of Surgifoam in critical surgical procedures and give my conclusion.

The current regulatory status in EU is

that it has a long product history of safety and effectiveness. We have had the product on the market for more than 40 years and, due to some changes in regulation, it was dropped prior to '96 and then the CE regulation came and we got it classified as CE Class III medical device in December of 1996.

Right now there is discussion in EU about reclassification borderline products into drugs, meaning that products like ours might have an impact and could become a drug again.

The current regulatory status in the United States is the fact that Ferrosan, in March '97, submitted an IDE, and over the next years we performed extensive clinical trials on humans, and they were multicenter trials. In 1999, based on the outcome of these clinical trials, we submitted the PMA to FDA, had the inspection in August of '99 and got the license to export products to the United States in September of '99.

Since 1999 we have submitted an amendment to this PMA several times. The new license has been granted based upon clinical studies on humans as well as clinical trials on animals and, of course, by use of design controls and risk

management.

Ferrosan has achieved a commission also for usage during neurological surgery. For achieving that authorization, we got some preclinical data as well as clinical trials and filed for getting information for use in our logical procedures. As you are, of course, aware elevated sensitivity to toxic and infective agents and the gelatin could be an infectious agent if not treated right. About toxicity, I am also talking about endotoxin testing which we are performing both on raw materials, as well as the finished products. During neurological surgery there is a potential for physical damage and there are fewer choices for adjunctive hemostasis.

The surgical product consists of gelatin, water and nitrogen. Surgifoam is a very safe product and we have had no MDRs in the years that we have supplied product to the U.S. market. But this is only caused by the additional quality control measurements that we have had since the USP standards that are right now in place don't fulfill all the requirements that we feel must be in place.

When we are searching for raw materials, and please recall that the gelatin is a very

complex biological raw material, we must make sure that our pig skin gelatin is not deteriorated by bovine originated gelatin or by alkaline based gelatin. We have required that the animal supplying the gelatin has been subjected to both pre- and postmortem veterinary controls, and that this is stated in the veterinary certificate accompanying each batch of the gelatin. We have required that the supplier certify that the gelatin is an accordance to an EC standard as regards manufacturing of these materials.

We are using a safe but also sensitive method for sterilization of the finished product. When I am talking about sensitive, it is dry sterilization in comparison to sterilization using formaldehyde. We are working on stringent hygienic and very low microbial conditions during the manufacturing of the sponges.

As we have had products on the European market for more than 40 years, we feel it is safe, and we felt safe about our products though we did agree with the FDA on the list of requirements put forward when we issued the IDE in 1997. We performed extensive clinical trials in '99 and it seems as if a lot has changed during these two

years.

We don't feel that the current standards control all the critical elements for gelatin hemostats. So, we don't feel, from a Ferrosan point of view, that reclassification is appropriate as long as there is no proper guidance and controls. Thank you very much.

DR. WHALEN: Questions for Ms. Bobak? Dr. Newburger?

DR. NEWBURGER: With all of the furor about spongiform encephalopathy that seems to have swept Europe, I assume with the herd and animal controls that is looked at as well?

MS. BOBAK: Yes, definitely. But since our gelatin is originated from pig skin, we don't have the BSE impact on the products but, of course, we must make sure that our gelatin has no contact at all to bovine-originated gelatin, and the guidance in Europe is to control that issue which we, of course, follow very stringently.

DR. WHALEN: This product has been in clinical use for how long?

MS. BOBAK: Forty-eight years.

DR. WHALEN: Certainly in my medical school years it was nothing new. I remember seeing

it in the operating room and that was in the early '70's. There is a multitude of manufacturers of it?

MS. BOBAK: Yes and no. In the U.S. there is manufacturing of a gelfoam product. In Europe there is actually our manufacturer of a sponge, Curacel. Then there are some in China and in India which is sterilized and manufactured in strange ways. So, I won't say many but there are some, yes.

DR. WHALEN: And over the several decades that it has been in existence, has there been any scientific advance or manufacturing change that has made a substantial increment in the effectiveness that you perceive?

MS. BOBAK: We have changed our manufacturing procedures several times. We have had--how do you say that in English?--something that changed the surface of the product. We had sodium laurel sulphate in the product twenty years ago. We changed that because we found out, doing other precautions during our manufacturing process, that it wasn't necessary to have that. Twenty-five years ago we had formaldehyde as a sterilization agent. We have omitted that completely. So, from

a Ferrosan point of view, we have definitely made more stringent our manufacturing process a great deal over the years.

DR. MILLER: So you, and I think Dr. Paulson also before you, seem to be not in favor of reclassifying this to a lower classification than it is now. Is that what I am to understand?

MS. BOBAK: I would answer yes and no, if I may. I can, of course, see something positive in a declassification but as long as there is no guidance document stating all the additional quality control elements that must be in place, or not having any risks to the consumer, then I am not in favor of a declassification on the sponges, no.

DR. WHALEN: Dr. Choti?

DR. CHOTI: The comparisons between the two products, they are both hemostatic agents but prepared very differently and they are very different products. Tell us a little bit about the mechanism of action of the gelatin sponge versus the cellulose product we have just heard about.

MS. BOBAK: I am sorry, I don't think I would be the right person to answer that question.

MS. GORMAN: Hi. My name is Anne Gorman, from Johnson & Johnson. Both products have very

similar mechanisms of action in that they act as surfaces on which platelets can be bound, the gelatin being more specific, Surgicel being less specific. Gelatin has a specific binding site for the platelets. With the Surgicel it is more of a physical phenomenon and once platelets are activated you have coagulation activation and clot formation.

DR. WHALEN: Thank you, Ms. Bobak.

MS. BOBAK: Thank you.

DR. WHALEN: Now we will continue with Ms. O'Grady's presentation.

MS. O'GRADY: Good afternoon. I am Judy O'Grady, senior vice president of regulatory, quality and clinical affairs for Integra LifeSciences Corporation.

I would like to thank the Food and Drug Administration and all the members of the General and Plastic Surgery Devices Panel for allowing me the time to speak at this public advisory committee regarding the reclassification of transitional Class III devices, the absorbable hemostatic agent and dressing devices intended for hemostasis during surgical procedures.

I will try to keep within the fifteen